REMARKS

Claims 1 and 3 are amended. Claims 13-18 are withdrawn from consideration. As a result, claims 1-12 are now pending in this application. Support for the amendments to the claims are found throughout the specification as filed (See page 8, Example 2, lines 14-17 with Figure 1). No new matter has been added. In view of the above amendments and following remarks, Applicants request withdrawal of the rejections in the Office Action dated February 18, 2011.

Claim Rejections - 35 U.S.C. §112:

Claims 3-6 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Examiner states that the instant claim 3 is unclear because the metes and bound of the claim cannot be determined and that it is unclear whether it is optional to mix the granules with excipients AND form a solid dosage form, or whether it is only optional to mix the granules with the excipients. Applicants have amended claim 3 wherein the phrase "optionally" has been omitted; the rejection is therefore moot. Claims 4-6 are dependent on claim 3, rejections of these claims are therefore, also moot. In view of the above amendments and remarks, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. §112.

Claim Rejections - 35 U.S.C. §103(a) for Obviousness

Claims 1-12 are rejected under 35 U.S.C. §103(a) as being unpatentable over WO 2004/010998 (AMIDON, 2003) in view of WO 1997/27198 (ARZENO, 1997); DRUG MONITOR; HANCOCK; U.S. Patent No. 6,660,303 (STANIFORTH, 2003); U.S. Patent No. 5,427,799 (VALENTINE, 1995) and as evidenced by U.S. Publication No. 2007/0129385 (SHARMA, 2005) and the definition of crystallization by the Encyclopedia Britannica.

Applicants would like to point out certain erroneous assumptions that the examiner has made.

1. On page 4, second full paragraph, of the Office Action, the Examiner says "Table 3 of Example 3 of AMIDON discloses a sustained release tablet that was formed by compression in a tabletting machine after all dry reagents were mixed (i.e. the tablet

was formed via direct compression in a dry process; paragraphs 85 and 117; instant claim 7). No "wet" reagents were used" (emphasis added).

Applicants submit that AMIDON does NOT disclose a dry process, wherein all dry agents are used. All examples disclosed by AMIDON use pregelatinized starch, which is a "wet" reagent. Pregelatinized starch is made from starch by partial hydrolysis followed by drying. It retains up to 15% water. The United States National Formulary, Edition 29 (2011) monograph (which is submitted herewith for reference) sets the Loss on Drying limit for pregelatinized starch at 14% w/w. Thus, pregelatinized starch cannot be considered 'dry' and any process that uses pregelatinized starch cannot be characterized as a 'dry process'. The present application does not mention pregelatinized starch anywhere. The Examiner avers in the same paragraph "[a]nd the binder, pregelatized starch (instant claims 2 and 9-12)." This is clearly incorrect attribution. While claim 2 mentions a binder, it does not mention pregelatinized starch at all. Similarly, claims 9 & 10 respectively list starch as a possible binder or a disintegrant, they do not list pregelatinized starch. Claims 11 & 12 do not mention any starch. Thus, the compositions disclosed by AMIDON and in the present application are different. AMIDON is therefore not an appropriate reference to be used when discussing dry processes.

2. On page 5, second paragraph, of the Office Action, the Examiner says "While not explicitly stated that the method taught by ARZENO embraces amorphous as well as crystalline valganciclovir, it is observed that Example 6 of ARZENO discloses a process of forming valganciclovir hydrochloride by attaching the hydrochloride ion to the N-CBZ-monovaline-monobenzyl-ganciclovir through use of a palladium hydroxide catalyst (page 48, last paragraph)...Thus, ARZENO teaches that a solid was formed (page 48, last paragraph). More isopropyl (sic) was added and the mixture was stirred, cooled, filtered and dried (page 49, paragraph 1)." The examiner goes on to say in the same paragraph "[a]nd removing the solvent to achieve amorphous valganciclovir hydrochloride (SHARMA, paragraphs 20 and 21)."

Applicants would like to bring to the Examiner's notice that ARZENO does not contemplate amorphous valganciclovir hydrochloride at all. Contrary to what the Examiner has said, it explicitly mentions formation ONLY of crystalline valganciclovir hydrochloride. On page 39, lines 1-3, ARZENO specifically mentions that the use of crystalline form has many advantages over the non-crystalline form. This clearly shows that ARZENO is in fact teaching away from the use of amorphous valganciclovir hydrochloride. Example 6, the only example for the preparation of valganciclovir hydrochloride that ARZENO discloses and which the Examiner has cited, says, at page 48 line 30 to page 49 line 1 "Isopropanol (35 ml) was added and the mixture was stirred vigorously to initiate crystallization....The product was collected by filtration" (emphasis added). It is quite obvious that this example is for the preparation of crystalline valganciclovir hydrochloride. SHARMA teaches a very specific method for the preparation of amorphous valganciclovir hydrochloride from a solution. This process involves spray-drying or vacuum-distillation (see paragraph [22] of SHARMA). The Examiner has used a rather broad term "removing the solvent" to describe this. The term "removing the solvent" means any process where solvent is removed from a solution or a suspension. This could involve filtration, decantation, centrifugation, distillation, layer separation, and several other techniques. The nature of the product obtained through such a process – whether crystalline or amorphous – is very technique dependent and cannot be generalized. SHARMA discloses that spray-drying a solution of valganciclovir hydrochloride provides amorphous valganciclovir hydrochloride. In this case, removal of the solvent – the reaction medium – results in the separation of the product in amorphous form. There is no filtration involved. ARZENO, to the contrary, provides a process for the preparation of crystalline valganciclovir hydrochloride, from which solvent is removed by filtration. In this case, the product has already crystallized out in the reaction medium which is then removed by filtration. The processes described by ARZENO and SHARMA are not comparable in terms whether the product is crystalline or amorphous. ARZENO provides a crystalline product while SHARMA

provides an amorphous product. Therefore, the Applicants respectfully submit that ARZENO does not teach amorphous valganciclovir hydrochloride.

3. The Examiner has incorrectly formulated the problem to be solved by the invention as provision of a composition of valganciclovir hydrochloride with greater bioavailability. Rather, the problem to be solved is the provision of a formulation of amorphous valganciclovir hydrochloride that does not convert to crystalline over time, on storage.

   Rather, as described in paragraphs [0005] and [0016] of the specification of the present application, the problem was to find a way to formulate amorphous valganciclovir hydrochloride in a way that it did not crystallize. The propensity of amorphous valganciclovir hydrochloride to crystallize when exposed to water under certain conditions makes formulating it difficult and unpredictable. Any change in the polymorphic nature of the active ingredient that changes during formulation or on storage could have unacceptable regulatory consequences. This was the problem the Applicants set out to solve and have solved. In addition, Applicants also found that amorphous valganciclovir hydrochloride was a very fine and fluffy material, with relatively low bulk and tap density that makes it difficult to formulate into an acceptable dosage form. In the present invention, Applicants have developed dry process, i.e. dry granulation or direct compression, for the preparation of solid dosage forms that overcomes these problems.

WO 2004/010998 (AMIDON, 2003) describes sustained release tablets of specifically sumanirole maleate, pramipexole dihydrochloride monohydrate or reboxitine succinate (See Examples 3-9, 11 on Pages 30-36). Besides, AMIDON discloses about 250 other active pharmaceutical agents with one or more of salts (See Pages 7-14). As the Examiner has pointed out, AMIDON does not teach that valganciclovir hydrochloride is amorphous as set forth by claim 1; inclusion of microcrystalline cellulose as set forth by instant claim 8; steps of mixing amorphous valganciclovir hydrochloride with pharmaceutical excipients, compacting the mixture by roller compactor, milling into granules, and then forming into a solid dosage form which is a

capsule or a tablet as set forth by instant claims 3-6. As discussed above, Applicants believe that AMIDON does not disclose or even suggest the presently claimed dry process for preparation of solid dosage forms comprising amorphous form of valganciclovir hydrochloride subject of the present claims and any claim rejection in view of AMIDON should be withdrawn.

As discussed above, ARZENO does not explicitly disclose valganciclovir hydrochloride in amorphous form. ARZENO uses a mixture of water and isopropanol for purification of valganciclovir hydrochloride via crystallization (page 48, last paragraph, line 32). This is further evidenced by disclosure of U.S. 6,083,953 (NESTOR) which discloses preparation of crystalline valganciclovir hydrochloride (column 23; line 59 through column 24; line 8) as cited in ARZENO. In NESTOR, the end product valganciclovir hydrochloride is crystallized from water and isopropanol mixture to get the crystalline product. Thus, it is clear that that ARZENO discloses crystalline valganciclovir and not amorphous valganciclovir hydrochloride. The Examiner's reliance on SHARMA in support of ARZENO as evidence is also misplaced. MPEP 2141.02 requires a prior art reference to be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). The examiner has referred to paragraphs [20] and [21] of SHARMA, which describe a process for preparing amorphous valganciclovir hydrochloride. As discussed above, ARZENO does not teach a process to prepare amorphous valganciclovir hydrochloride. Therefore, it is requested that rejection of claims with respect to ARZENO be withdrawn.

The Examiner has said that the claimed invention is obvious over DRUG MONITOR in view of HANCOCK. DRUG MONITOR is a defunct website (not updated since 2002), which disclaims the data and information provided therein. Also, since it is a site maintained by a private individual, and does not cite any authoritative source for the data provided in the site, the data provided by DATA MONITOR cannot be considered authoritative or reliable. In any case, the Examiner has concluded that there was a known problem in the art with regard to the bioavailability of valganciclovir that members in the field were endeavoring to solve on the basis of the disclosure in DRUG MONITOR. In fact, DRUG MONITOR does not say anywhere that there was a problem with the bioavailability of valganciclovir. It merely states that high fat food

significantly increases the bioavailability of valganciclovir, indicating that there is a possible food-effect. As discussed above, the invention described and claimed in the present application is not on increasing the bioavailability of valganciclovir hydrochloride. The application mentions bioavailability only in the context of discussing the background. HANCOCK provides a general discussion on the choice of crystalline and amorphous state of pharmaceutical systems, including a mention on the use of amorphous systems as a means to enhance dissolution and bioavailability. It does not discuss any specific product, including valganciclovir hydrochloride. Therefore, Applicants respectfully submit that neither DRUG MONITOR nor HANCOCK is relevant to the invention claimed in this application.

The Applicants believe that though the amorphous form may improve solubility and bioavailability, the issue of stability and any related inter-conversion between the forms becomes paramount in this case. HANCOCK (see page 2, first column, first paragraph) also identifies the problem associated with amorphous forms.

> "We would also expect amorphous systems to exhibit greater chemical reactivity and to show some tendency to spontaneously crystallize, possibly at different rates below and above *Tg*. From a pharmaceutical perspective we have an interesting situation. The high internal energy and specific volume of the amorphous state relative to the crystalline state can lead to enhanced dissolution and bioavailability,4 but can also create the possibility that during processing or storage the amorphous state may spontaneously convert back to the crystalline state."

STANIFORTH describes an augmented superdisintegrant having improved compactability, methods of obtaining the same and solid dosage forms comprising this novel augmented superdisintegrant and an active agent. The Examiner states that STANIFORTH teaches the state of the art of direct compression. The present invention does not relate to the use of any such superdisintegrant in the dry process method that is being employed for the preparation of solid dosage forms of amorphous valganciclovir hydrochloride.

VALENTINE describes sustained release dosage forms of active ingredients and methods for producing the same. Since the references cited by the examiner do not disclose amorphous

valganciclovir hydrochloride, both STANIFORTH and VALENTINE, either alone or in combination with other references, do not make the invention obvious.

As stated in the instant specification (paragraph [005]), Applicants have additionally found that amorphous valganciclovir hydrochloride is very fine and fluffy material, with relatively low bulk and tap density. Such materials are difficult to formulate using dry processes, as achieving desirable content uniformity, hardness, friability, etc. is difficult. The conventional way to tackle this problem during formulation is to use wet granulation process, which tends to damp down fluffy material. But, as discussed above, wet granulation process or "wet" excipients cannot be used due to the instability of the amorphous material. The challenge, therefore, was to develop a stable dosage form of amorphous valganciclovir hydrochloride with uniformity of weight, sufficient hardness and friability and other desirable tablet properties, using a dry process. In the present invention, applicants have successfully and advantageously utilized the dry process for the preparation of a stable solid dosage form of amorphous valganciclovir hydrochloride wherein the amorphous form does not convert to the crystalline form and the resultant dosage form has desirable tablet properties.

The examiner has further rejected certain claims citing KSR International Co. v. Teleflex Inc. 550 U.S. 398, 127 S. Ct. 1727, 82 USPQ2d 1385, 1395-97 (2007)

> Exemplary rationales that may support a conclusion of obviousness include:
>
> (A) Combining prior art elements according to known methods to yield predictable results;
> (B) Simple substitution of one known element for another to obtain predictable results;
> (C) Use of known technique to improve similar devices (methods, or products) in the same way;
> (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
> (E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
> (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
> (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

The Examiner states that with regard to instant claim 1, at least rationales (A and C) of KSR International Co. v. Teleflex Inc. may be employed and that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the method taught by AMIDON by substituting the active agent taught by AMIDON with the amorphous valganciclovir hydrochloride taught by ARZENO because AMIDON teaches that valganciclovir hydrochloride is a suitable active agent for use in the sustained release tablet of the invention. As stated earlier, AMIDON does not use dry excipients and ARZENO does not teach amorphous valganciclovir hydrochloride, so at least rationales (A and C) do not make claim 1 as amended obvious.

The examiner further states that with regard to claim 8, at least rationale (D) of KSR International Co. v. Teleflex Inc. may be employed. The examiner believes that it would be obvious to have modified the method taught by AMIDON by substituting adding microcrystalline cellulose to the tablet formulation because the method utilized in AMIDON is direct compression method and microcrystalline cellulose is a direct compression tabletting excipient which is generally considered to exhibit superior compressibility and disintegration properties as taught by STANIFORTH. The applicant believes that this rejection is based on impermissible hindsight. AMIDON does not use dry excipients nor does it mention any specific formulation of amorphous valganciclovir hydrochloride, which has problem of conversion to crystalline form overtime. Both AMIDON and STANIFORTH either alone or in combination do not identify this problem of stability as identified in claim 8 which has ultimate dependency on currently amended claim 1. The examiner is therefore requested to withdraw the rejection.

The examiner with regard to instant claims 3-6 believes that at least rationales (C and D) make the invention obvious. He says "[I]t would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to have modified the method of forming a sustained release tablet taught by AMIDON by utilizing the steps of mixing an active agent with xanthan gum (i.e. excipient), and other excipients, roller compacting, milling into particles and then formulating into tablets or capsules as taught by VALENTINE to produce sustained release dosage forms because AMIDON teaches that the formulation of his invention are sustained release formulations and VALENTINE teaches the above steps as a method to form

sustained release capsules and tablets." The applicant believes that this rejection is based on hindsight. AMIDON does not teach amorphous valganciclovir hydrochloride which has problem of conversion to crystalline form overtime. Both AMIDON and VALENTINE, either alone or in combination, do not identify this problem of stability as identified in Claims 3-6. The examiner is therefore requested to withdraw the rejection.

"A statement that modifications of the prior art to meet the claimed invention would have been well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teachings of the references. *Ex parte* Levengood, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). (See MPEP 2143.01 (IV)) (KSR, 550 U.S. at ___, 82 USPQ2d at 1396)".

Therefore, none of the cited references disclose amorphous valganciclovir hydrochloride nor discuss the problems associated with the amorphous form of valganciclovir hydrochloride. Nothing in any of these cited references suggest that using a dry process would provide the necessary solution for the problems associated with amorphous form of valganciclovir hydrochloride. Quite simply, none of the references provide any expectation that using a dry process for preparing dosage forms of amorphous valganciclovir hydrochloride would provide the necessary protection for amorphous form.

The Office Action also concludes that invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by references. Applicants respectfully disagree. Applicants have realized the need for using amorphous form of valganciclovir hydrochloride and then successfully discovered a process for formulating the same into an acceptable solid dosage form. Applicants respectfully assert that the currently amended claim 1 is not obvious in view of the cited reference. Dependent claims 2-12 are likewise not obvious in view of the cited references for the same reason. In view of the above amendments and remarks, Applicants respectfully request withdrawal of rejections under 35 U.S.C. §103 and issue allowance of claims 1-12.

Conclusion:

For the foregoing reasons, the Applicants submit that the present invention is now in condition for allowance. Allowance of all pending claims is respectfully solicited.

Authorization is hereby given to charge any fees deemed to be due in connection with this Response to Deposit Account No. 50-0912.

Respectfully submitted,

SINGH et al.

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